

**REMARKS**

I. The outstanding issue in the instant application is:

- Rejection of claims 1-32 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Pat. No. 4,689,322 to Kulbe et al.

II. 35 U.S.C. § 102(b)

A. Rejection over Kulbe et al.

The Examiner asserts that claims 1-32 are anticipated by U.S. Pat. No. 4,689,322 to Kulbe et al. (hereinafter referred to as "Kulbe et al."). Applicants respectfully traverse.

Kulbe et al. teaches a pharmaceutical product which contains at least a calcium salt or a calcium mixed salt of a natural or chemically modified polymeric, anionic carboxylic acid and/or an ester of sulfuric acid, and additive materials and/or an ester of sulfuric acid, and additive materials and/or carrier materials. The polymeric, anionic carboxylic acid is taught to include polygalacturonic acid (col. 3, lines 50-53). The Examiner alleges that the teaching of polygalacturonic acid as the anion of the therapeutic calcium salt of Kulbe et al. teaches Applicants' claimed invention directed to glutarate as the anion of the therapeutic calcium salt.

In order for a reference to be asserted under 35 U.S.C. § 102, it must teach each and every element of the instant claimed invention. "A claim is anticipated only if **each and every element** as set forth in the claim is found either expressly or is inherently described in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987) (emphasis added). "The identical invention **must be shown** in as complete detail as is contained in the...claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989) (emphasis added). See also MPEP 2131.

Applicants assert that one of ordinary skill in the art is aware that the polygalacturonic acid compound of Kulbe et al. is structurally different from the glutarate of Applicants' invention. The molecular structure and/or molecular formula of calcium glutarate is given in the instant specification on page 15 and in original claim 15. The molecular structure of poly-D-galacturonic acid is shown in Kulbe et al., col. 8 (also referred to as pectic acid), a copy of which is provided in Appendix B. Thus, Applicants assert that a calcium salt of a

**polymeric, anionic carboxylic acid** (e.g., polygalacturonic acid) as taught by Kulbe et al. **does not** teach or suggest the calcium salt of an **anionic dicarboxylic acid** (e.g., glutarate) as taught by Applicants.

Applicants further assert that Kulbe et al. teaches that the calcium salt or mixed calcium salt of their invention must be a polymeric, anionic carboxylic acid:

“In accordance with the present invention the calcium salts of natural or chemically modified polymeric, anionic carboxylic acids or esters of sulfuric acid are used.” (col. 6, lines 39-41)

Kulbe et al. discloses specific polymeric, anionic carboxylic acid compounds that are acceptable for their therapeutic calcium salt, and all of these embodiments are polymers (see, col. 6, line 46 to col. 8, line 68). Again, referring to the structures of polygalacturonic acid as compared to glutarate, one of ordinary skill in the art recognizes that glutarate is not a polymeric, anionic carboxylic acid.

Applicants assert that Kulbe et al. does not teach or suggest, either expressly or inherently, each and every element as set forth in the claimed invention and, consequently, cannot serve as a basis for an anticipation rejection. Therefore, Applicants submit that the instant invention is novel and respectfully requests withdrawal of the rejection under 35 U.S.C. §102 over Kulbe et al.

### CONCLUSION

Applicants have amended the specification to correct for typographical and/or grammatical errors. Therefore, Applicants assert that these amendments do not narrow the scope of the claims within the meaning of *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 234 F.3d 558, 586, 56 USPQ2d 1865, 1886 (Fed. Cir. 2000). Applicants further assert that no new matter has been added. A marked version of the amendments to the specification submitted herein are provided as Appendix A.

Applicants believe that the claimed invention is novel and, for reasons provided herein, that the rejection under 35 U.S.C. §102(b) over Kulbe et al. should be withdrawn. For the Examiner's convenience, a copy of all claims pending in the instant application are provided in Appendix C.

Applicants have submitted herewith, a petition to revive under 37 C.F.R. § 1.137 and the petition fee set forth in 37 C.F.R. § 1.17(m). Applicants believe that no other fees are due with this filing, however, if Applicants are in error, the Commissioner is authorized to draw any deficiency in fees or credit any overpayment in this matter from Deposit Account 06-2375, under Order No. P02490US0, from which the undersigned is authorized to draw.

If questions arise regarding the submission of this response, the Examiner is invited to contact the undersigned to expedite a resolution.

Dated: June 27, 2002

Respectfully submitted,

By Elizabeth A. Hart  
Elizabeth A. Hart, Registered Patent Agent  
Registration No.: 50,931  
FULBRIGHT & JAWORSKI L.L.P.  
1301 McKinney, Suite 5100  
Houston, Texas 77010-3095  
(713) 651-5698

**APPENDIX A****Version With Markings to Show Changes Made to Specification****1. Page 8, first paragraph:**

A primary aim of prophylactic and therapeutic measures in patients with renal osteodystrophy is therefore to lower the level of serum phosphate below a threshold value of 1.8 mmol/l (5.6 mg phosphorus/dl). A dietary restriction of the phosphate intake and thereby an effective lowering of the level of serum phosphate is limited if [it] not impossible in long-term therapy since there is the risk of an inadequate protein intake and thus of malnutrition. Thus for example on an average dietary phosphate intake of 3.8 to 4.7 g/day only about 1 g phosphate per day can be eliminated by dialysis (hemodialysis or peritoneal dialysis). Thus the patients have an undesired positive phosphate balance despite the restriction (Hercz, G. et al., Kidney Int. Suppl. 22 (1987), 215-220).

**2. Page 8, second paragraph:**

For this reason phosphate binding agents that can be administered orally are preferably used as therapeutic agents which are intended to prevent the resorption of food phosphates in the gastrointestinal tract. Known substances with phosphate-binding properties are the calcium salts calcium acetate, calcium carbonate, calcium citrate, calcium alginate, calcium gluconate, calcium lactate and calcium sulfate[]], magnesium carbonate and magnesium hydroxide as well as aluminum hydroxide and aluminum carbonate. However, not all of these salts have gained therapeutic importance or been considered safe or efficacious. Aluminum hydroxide, calcium carbonate and calcium acetate have been used. However, these agents for enteric phosphate restriction may have undesired side effects. Thus when  $Al^{3+}$  compounds are administered chronically a microcytic anemia or encephalopathy can develop with a very poor prognosis or osteopathy can occur. A possible disadvantage of a long-term therapy with calcium salts is the development of hypercalcemia which is associated with calcification of blood vessels and soft tissues and gastrointestinal complaints (Dialysis Journal 37 (1991), 1-40).

**3. Page 9, first paragraph:**

In addition Burt, H. M. et al. (J. Pharm. Sci. 75 (1987), 379-383) describe anion exchangers which carry tertiary or quaternary amines as the functional group and adsorb

inorganic phosphate in the intestinal tract. However, it is known that strongly basic anion exchangers such as for example cholestyramine (Johns, W. H., Bates, T. R., J. Pharm. Sci 59 (1970), 788 ff.) may undesirably bind bile acids and hence their long-term use leads to hypovitaminosis.

**4. Page 9, second paragraph, ending on page 12:**

A common treatment for phosphorus retention is disclosed in U.S. Pat. No. 4,870,105, entitled Phosphorus binder, which discloses a calcium acetate phosphorus binder for oral administration to an individual for the purpose of inhibiting gastrointestinal absorption of phosphorous. It further discloses a method of inhibiting gastrointestinal absorption of phosphorous, comprising administering orally the calcium acetate phosphorus binder, preferably close in time to food and beverage consumption. However, side effects [affects] of calcium acetate may include acetic acid breath, stomach upset and gastrointestinal discomfort. Other alternatives for treating phosphorus retention are shown in the following United States patents. U.S. patent No. 6, 160,016 entitled Phosphorus binder, discloses a calcium formate composition for oral administration to an individual for the purpose of inhibiting gastrointestinal absorption of phosphorous[ is disclosed]. It further discloses a method of inhibiting gastrointestinal absorption of phosphorous, comprising administering orally the composition, preferably close in time to food and beverage consumption[ is also disclosed]. U. S. patent No. 6,103,709 entitled Therapeutically effective  $1\alpha,25$ -dihydroxyvitamin D<sub>3</sub> analog [analo], discloses a method for treatment of diseases caused by deficiency or overproduction of the vitamin D<sub>3</sub> metabolites by administering analogues of  $1\alpha[. ],25$ -dihydroxyvitamin D<sub>3</sub>. These are disclosed to be analogues that are selective agonists or antagonists for the genomic and rapid nongenomic cellular responses. It further discloses a pharmaceutical composition comprising  $1\alpha[. ],25$ -dihydroxyvitamin D<sub>3</sub> analog. U.S. patent No. 5,939,406 entitled 18-substituted-19-nor-vitamin D compounds, discloses a class of vitamin D compounds, namely, 13-ethyl and 13-vinyl-18,19-dinor-vitamin D derivatives, as well as a general method for their chemical synthesis. The compounds have the formula:  $C_{17}H_{22}O_2RR_6Y_1Y_2$ , where  $Y_1$  and  $Y_2$ , which may be the same or different, are each selected from the group consisting of hydrogen and a hydroxy-protecting group,  $R_6$  is selected from the group consisting of an ethyl or vinyl radical, and where the group R represents any of the typical side chains known for vitamin D type compounds. These 18-substituted compounds are characterized by minimal intestinal calcium transport activity and

minimal bone calcium mobilization activity resulting in novel therapeutic agents for the treatment of second hyperparathyroidism. These compounds also are disclosed as exhibiting pronounced activity in arresting the proliferation of undifferentiated cells and inducing their differentiation to the monocyte thus evidencing use as anti-cancer agents and for the treatment of diseases such as psoriasis. U. S. patent No. 5,753,706 entitled Methods for treating renal failure, discloses a method of controlling phosphate metabolism and metabolic acidosis in patients suffering from renal failure and associated hyperphosphatemia or patients predisposed to development of a hyperphosphatemic condition[ are provided]. The method comprises administering to a patient a ferric-containing compound selected from the group consisting of ferric citrate, ferric acetate, and combinations thereof. It discloses that a therapeutic benefit can be realized in accordance with such method by administering the compound orally to a patient to contact and bind with ingested phosphate in the patient's digestive tract, and thereby prevent its intestinal absorption. U.S. patent No. 5,597,815 entitled Prevention of hyperphosphatemia in kidney disorder patients [patie], discloses that 19-nor-vitamin D analogs, and particularly 19-nor-1  $\alpha$ ,25-dihydroxyvitamin D<sub>2</sub>, possess low calcemic and phosphatemic activity while also having the ability to suppress parathyroid hormone (PTH) production. It further discloses that the suppressive effect on PTH secretion of these 19-nor analogs without significant changes in serum calcium or serum phosphorus make them ideal tools for the treatment of secondary hyperparathyroidism in patients having kidney disorders. U. S. patent No. 4,308,264, entitled Stabilized, dilute aqueous preparation of [1,25-dihydroxy] 1 $\alpha$ ,25-dihydroxycholecalciferol for neonatal administration, discloses 1 $\alpha$ ,25-Dihydroxycholecalciferol, also known as 1 $\alpha$ ,25-dihydroxyvitamin D<sub>3</sub>, calcitriol or 1 $\alpha$ ,25(OH)<sub>2</sub>D<sub>3</sub>, that occurs naturally in man as the active form of cholecalciferol or vitamin D<sub>3</sub>. It further discloses that the natural supply of vitamin D<sub>3</sub> depends on the conversion of 7-dehydrocholesterol to vitamin D<sub>3</sub> in the skin by ultraviolet light. Vitamin D<sub>3</sub> is then converted to calcitriol in a two-step process in the liver and kidney before its acts on its target issue. U.S. patent No. 6,103,126, entitled Process for the selective elimination of inorganic phosphate from liquids by means of absorbent materials modified with polynuclear metal oxhydroxides, discloses the use of an adsorbent material modified with polynuclear metal oxhydroxides for the selective elimination of inorganic phosphate from liquids, in particular from body fluids containing protein such as whole blood, plasma, liquid contents of the intestine as well as from dialysis fluid, as well as a process for the production of a pharmaceutical agent for oral application for the selective removal of inorganic phosphate in

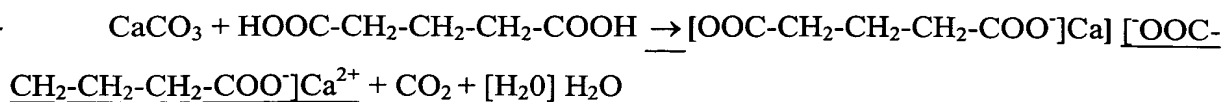
which an adsorbent material used is coated with a layer resistant to gastric acid or dispensed into an acid-resistant capsule. It further discloses that in order to selectively eliminate inorganic phosphate in an extracorporeal perfusion system, a body fluid such as whole blood or plasma is passed over one of the adsorbent materials. U.S. patent No. 4,689,322, entitled Pharmaceutical products, calcium mixed salts of polymeric, anionic carboxylic acids and/or their esters of sulfuric acid, and methods for their preparation and use, discloses a pharmaceutical product which contains at least a calcium salt or a calcium mixed salt of a natural or chemically modified polymeric, anionic carboxylic acid and/or an ester of sulfuric acid, and additive materials and/or an ester of sulfuric acid, and additive materials and/or carrier materials. There are further disclosed calcium salts, and methods of preparation thereof, comprised of polymannuronic acid, polygalacturonic acid, polyglucuronic acid, polyguluronic acid, the oxidation products of homoglycans, the oxidation products of heteroglycans, or their mixtures, for controlling the levels of phosphate, calcium and iron in patients with chronic uremia and/or the control of the oxalate and/or phosphate of the blood in kidney stone prophylaxis.

**5. Page 13, second paragraph, titled 'Summary of the Invention':**

A method for inhibiting gastrointestinal absorption of phosphorous in an individual, comprising orally ingesting a quantity of calcium glutarate sufficient to bind with phosphorous in the gastrointestinal tract. The calcium glutarate is present in an amount sufficient to provide between about 400mg to about 1500 mg of calcium as calcium glutarate. The calcium glutarate may be in tablet form, gelatin capsule form, effervescent form or in liquid form. The calcium glutarate may be administered at mealtime. An orally administerable pharmaceutical composition is used [for use] in the treatment of hyperphosphatemia and for preventing the formation of phosphate- and oxalate-containing kidney stones which comprises as the principal active ingredient a therapeutically effective amount of calcium glutarate combined with a pharmaceutically acceptable carrier in the form of beads, tables, liquid, capsules, powders, dragees or pills.

**6. Page 15, second full paragraph:**

The calcium glutarate has a density of about 0.65 gm/cc. It has about 21.6 per cent elemental calcium. Its formula is  $[\text{OOC-CH}_2\text{-CH}_2\text{-CH}_2\text{-COO}]\text{Ca}$ . The reaction for the formation of calcium glutarate is:



**7. Page 17, first full paragraph:**

The following in-vitro tests were conducted to test the solubility and ability of calcium glutarate to bind with phosphates. The tests included analysis for monobasic,  $\text{Ca}(\text{Na}_2\text{PO}_4)_2$  [ $\text{Ca}(\text{Na}_2\text{po}_4)_2$ ], dibasic,  $\text{CaNaPO}_4$ , and tribasic,  $\text{Ca}(\text{PO}_4)_2$  [ $\text{CA}_3(\text{PO}_4)_2$ ] binding. The three examples are as follows.

**8. Page 17, second full paragraph:**

An aqueous solution of calcium glutarate was mixed with a twice over molar solution of sodium phosphate. A suspension formed which was filtered by a vacuum through a 0.45- $\mu\text{m}$  [ $\mu\text{um}$ ] nylon filter. The resulting[:] filtrate was assayed for free calcium by atomic absorption spectrometry [spectrometry]. The percent of calcium recovered in solution was 0.1%. The test showed that almost all of the calcium was in the practically insoluble form of calcium phosphate.

**9. Page 18, first full paragraph:**

Calcium glutarate does not appear to form undesirable complexes. It has a pleasant taste so it [in] can be taken in the form of a [chewable] tablet, or it may [can] be taken as a liquid. Because of the ability of the calcium glutarate to easily and rapidly bind with the phosphates a relative small dosage is possible under usual circumstances. Calcium glutarate has the qualities that are desirable in binding phosphates. It is highly soluble so it [in] should be effective even when [that] there is little stomach acid. Virtually all of the calcium glutarate would appear to readily bind with available phosphates to form [an] insoluble salts that can be passed through a patient's digestive system. A reasonable excess of calcium glutarate beyond that needed to bind with free phosphates would appear to pose no problem and would be available to provide calcium to treat or prevent osteoporosis or other diseases that are treated with calcium supplements. It would also appear to not be a risk for the formation of kidney stones.

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**APPENDIX B****Kulbe et al., col. 8 Showing the Structure of Polygalacturonic Acid**

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4,689,322

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1. Galactomannans (guar gum = guaran; carboxyguar gum), (carob-gum = locust bean gum = carob bean gum).

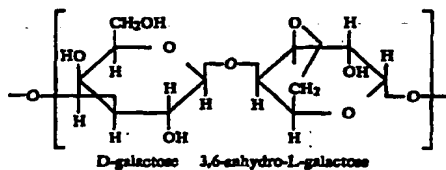
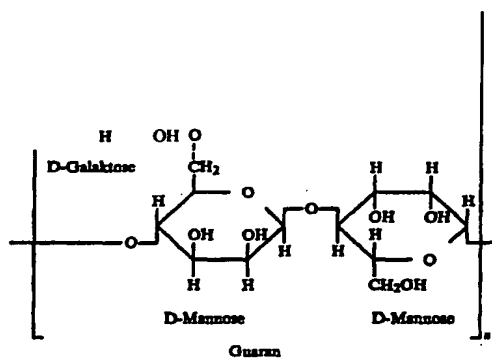
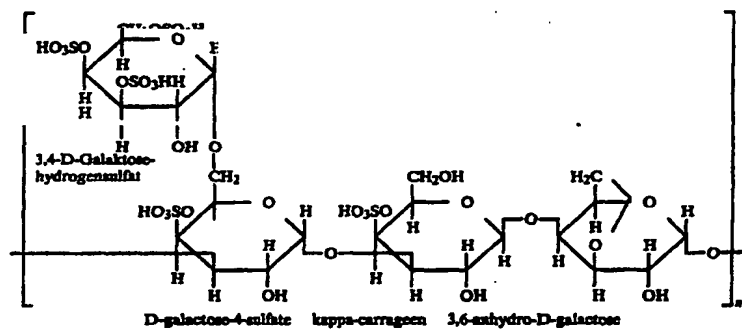
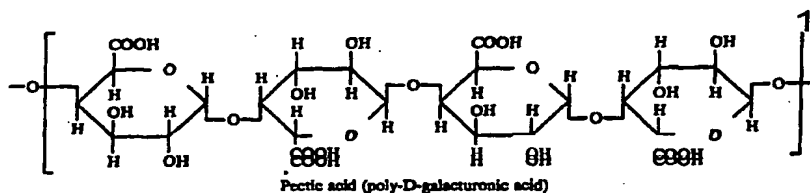
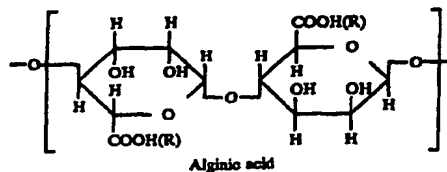
As well, mixtures of these compounds can be used. (D) Mixtures of the substances enumerated under (A) to (C) above.

2. Sulfate-esterified carrageens (kappa, i).

Several structural formulae of these compounds are

3. Chondromannans.

presented in the following:



**APPENDIX C**

**Clean Copy of All Pending Claims, as of June 27, 2002**

1. A method of inhibiting gastrointestinal absorption of phosphorous in a person, comprising: orally ingesting a quantity of calcium glutarate sufficient to bind with phosphorous in the gastrointestinal tract.
2. The method according to claim 1 wherein the calcium glutarate is present in an amount sufficient to provide between about 400mg to about 1500mg of calcium as calcium glutarate.
3. The method according to claim 1 wherein the calcium glutarate is in tablet form.
4. The method according to claim 1 wherein the calcium glutarate is in gelatin capsule form.
5. The method according to claim 1 wherein the calcium glutarate is in effervescent form.
6. The method according to claim 1 wherein the calcium glutarate is in liquid form.
7. A method of inhibiting gastrointestinal absorption of phosphorous in an individual, comprising: orally ingesting a quantity of calcium glutarate at a mealtime.
8. The method according to claim 7 wherein the quantity of calcium glutarate is present in an amount sufficient to provide between about 400mg to about 1500mg of calcium as calcium glutarate.
9. The method according to claim 7 wherein the quantity of calcium glutarate is in tablet form.
10. The method according to claim 7 wherein the quantity of calcium glutarate is in gelatin form.

11. The method according to claim 7 wherein the quantity of calcium glutarate is in effervescent form.
12. The method according to claim 7 wherein the calcium glutarate is in liquid form.
13. A pharmaceutical therapeutic composition in oral dosage form for controlling phosphate retention in patients having need for reduced absorption of dietary phosphate, said composition comprising sufficient calcium glutarate to bind with phosphorous in the gastrointestinal tract, and a pharmaceutically acceptable excipient for said oral dosage form.
14. The therapeutic composition according to claim 13 wherein the quantity of calcium glutarate is present in an amount sufficient to provide between about 400mg to about 1500mg of calcium as calcium glutarate.
15. The therapeutic composition according to claim 13 wherein the quantity of calcium glutarate is in tablet form.
16. The therapeutic composition according to claim 13 wherein the quantity of calcium glutarate is in gelatin form.
17. The therapeutic composition according to claim 13 wherein the calcium glutarate is in effervescent form.
18. The therapeutic composition according to claim 13 wherein the calcium glutarate is in liquid form.
19. An orally administerable pharmaceutical composition for use in the treatment of hyperphosphatemia and for preventing the formation of phosphate- and oxalate-containing kidney stones in humans which comprises as the principal active ingredient a therapeutically effective amount of calcium glutarate combined with a pharmaceutically acceptable carrier.

20. A pharmaceutical composition according to claim 19 particularly adapted for treating hyperphosphatemia and for preventing the formation of phosphate- and oxalate-containing kidney stones in which the calcium glutarate is present in the amount of about 400mg to about 1500mg of calcium as calcium glutarate.
21. A method of treating hyperphosphatemia and for preventing the formation of phosphate- and oxalate-containing kidney stones in humans which comprises orally administering to a person in need thereof a pharmaceutical composition according to claim 19.
22. A method of treating hyperphosphatemia and for preventing the formation of phosphate- and oxalate-containing kidney stones in humans which comprises orally administering to a person in need thereof a pharmaceutical composition according to claim 20.
23. A method of treating hyperphosphatemia and for preventing the formation of phosphate-containing kidney stones in humans which comprises orally administering to a person in need thereof a pharmaceutical composition according to claim 19.
24. A method of treating hyperphosphatemia and for preventing the formation of phosphate-containing kidney stones in humans which comprises orally administering to a person in need thereof a pharmaceutical composition according to claim 20.
25. A pharmaceutical compound for treating hyperphosphatemia and for preventing the formation of phosphate-containing kidney stones in humans of the formula: pharmaceutical grade  $[\text{OOC-CH}_2\text{-CH}_2\text{-CH}_2\text{-COO}]\text{Ca}$  in an amount sufficient to inhibit gastrointestinal absorption of phosphorous in a person, and a pharmaceutically acceptable carrier.
26. A method of treating hyperphosphatemia and for preventing the formation of phosphate-containing kidney stones in humans, which comprises administering to a mammal a phosphorous binding amount of the compound of claim 25.

27. A method of treating hyperphosphatemia, which comprises administering to a mammal a hyperphosphatemia treating amount of the compound of claim 25.
28. A therapeutic composition according to claim 25 wherein the quantity of calcium glutarate is present in an amount sufficient to provide between about 400mg to about 1500mg of calcium as calcium glutarate.
29. The therapeutic composition according to claim 25 wherein the quantity of calcium glutarate is in tablet form.
30. The therapeutic composition according to claim 25 wherein the quantity of calcium glutarate is in gelatin form.
31. The therapeutic composition according to claim 25 wherein the calcium glutarate is in effervescent form.
32. The therapeutic composition according to claim 25 wherein the calcium glutarate is in liquid form.